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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,296	05/25/2001	Eugene A. Woltering	98M06.1 Woltering	4311

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EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 08/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/866,296	Woltering et al.
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Jun 12, 2002*.

2a) ☐ This action is **FINAL.** 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1-37* is/are pending in the application.

4a) Of the above, claim(s) *14-37* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *1-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1. ✓ Notice of References Cited (PTO-892)
2. ✓ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. X Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4. ☐ Interview Summary (PTO-413) Paper No(s).
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Other

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DETAILED ACTION

Claims 1-37 are pending.

Election/Restriction

Applicants' election without traverse of the Group I invention (claims 1-13) in Paper No. 6 filed 6/12/2002 is acknowledged. Claims 14-37 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 1-13 are under examination in the instant office action.

Claim Rejections - 35 USC § 112

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered indefinite by the phrase "if any" with regard to angiogenic vessels (steps c and d) because it is uncertain what is "observing" or "measuring" in the absence of angiogenic vessels or what is the purpose of the process in the absence of angiogenic vessels. Further, it is uncertain as claimed what would be a "time sufficient to allow angiogenic vessels" to grow, if there are no neither angiogenic vessels nor source of angiogenic vessels in the incubating step (c).

Claim 2 is rendered indefinite by the phrase "substantially" as related to the presence of exogenous factors in a medium. It is unclear what amounts of factors are intended for the

"medium" and whether the "tissue sample" and "matrix" are "substantially" free from exogenous factors as intended. This claim is also confusing in the light of the other claims which are drawn to the use of serum (claim 3) and/or to the use of various factors (claims 4, 5 and 13).

Claim 10 is rendered indefinite by the phrase "Matrigel" which appears to be a trademark. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim 13 is indefinite with regard to "additional factor" because it is uncertain to what type of other (first) "factor", if any, the claimed "additional factor" is added. It is uncertain whether or not either first or additional factor(s) are derived from serum, matrix and/or tissue sample employed in the method of claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-10 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,856,184 [A].

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Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium supplemented with serum and/or various factors which enhance or suppress angiogenesis. Some claims are further drawn to the use of matrix such as fibrin, collagen, agar, or Matrigel. Some claims are further drawn to the use of various tissues in the method for assaying angiogenesis.

US 5,856,184 [A] discloses a method for assaying angiogenesis ex vivo wherein the method comprises step of embedding three-dimensional tissue samples of aorta segments in the Matrigel matrix, step of supplying the embedded tissue samples with a medium that supports growth of the tissue samples or with MCDB medium, step of incubating the embedded tissue samples in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue samples and step of observing or measuring the angiogenic vessels (col. 11, lines 15-40). The commercial Matrigel product contains fibrin, collagen, gelatin, agar or agarose. Although the cited patent is silent with regard to the presence or absence of serum in the commercial medium MCDB, it teaches the use of the three-dimensional system for observing and measuring differences in angiogenesis as the result of addition of various factors in the medium that supports growth such as various collagen fractions, for example. And , thus, the

cited method is considered to anticipate the presently claimed invention to the extend of using unidentified exogenous factors whether they are derived from serum or not as encompassed by the claims 2, 3 or 13.

Claims 1-6 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. [U].

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium with or without serum, to the use of medium supplemented with various factors including vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF) for observing differences in angiogenesis in various systems. Some claims are further drawn to the use of matrix such as fibrin.

Brown et al. [U] teaches a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue sample such as human placental blood vessel fragments a fibrin matrix, step of supplying the embedded tissues sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in

the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels as the result of addition of various factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) in the presence or absence of serum (see abstract and page 551, col. 1, lines 4-20). The cited reference anticipates all active steps and all structural elements of the presently claimed method.

Claims 1, 3, 4, 6, 7, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Montesano et al. [V].

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium supplemented with serum and/or with various factors which enhance or suppress angiogenesis. Some claims are further drawn to the use of matrix such as fibrin or collagen. Some claims are further drawn to the use of various tissues excluding tumor fragments and segments of artery or vein.

Montesano et al. [V] discloses a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue samples of muscular and adipose tissues in a matrix of fibrin gel or collagen gel, step of supplying the embedded tissue samples with a medium that supports the growth of the tissue samples or MEM medium with serum, step of incubating the embedded tissue samples in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue samples and step of observing or measuring the angiogenic vessels (see abstract, page 807 at section "Materials and Methods" and figures 1-2). The cited reference anticipates all active steps and all structural elements of the presently claimed method.

Claims 1, 4, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Lugassy et al. [W].

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium supplemented various factors which enhance or suppress angiogenesis. Some claims are further

drawn to the use of various tissues in the method for assaying angiogenesis including tumor tissues.

Lugassy et al. [W] discloses a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue sample such as angioma or tumor fragments a matrix, step of supplying the embedded tissue samples with a medium that supports growth of the tissue samples, step of incubating the embedded tissue samples in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue samples and step of observing or measuring the angiogenic vessels. The cited reference teaches that the disclosed three-dimensional *in vitro* or *ex vivo* tumor system allows for observing angiogenesis in malignant samples and production of metastases. Thus, the cited reference anticipates the presently invention as claimed and as intended.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,856,184 [A] taken with Brown et al. [U], Montesano et al. [V] and Lugassy et al. [W].

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Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium supplemented with serum and/or various factors which enhance or suppress angiogenesis. Some claims are further drawn to the use of matrix such as fibrin, collagen, agar, or Matrigel. Some claims are further drawn to the use of various tissues in the method for assaying angiogenesis including or excluding tumor or artery or vein fragments.

All cited references teach methods for assaying angiogenesis *ex vivo* as the presently claimed wherein the cited methods encompass the use of three-dimensional systems comprising tissue samples embedded into various matrix and supplied with various media supplemented with various growth factors which enhance or suppress angiogenesis as required by the presently claimed. All cited references teach the disclosed systems as models for *ex vivo* measuring, observing and assaying angiogenesis. Some cited references demonstrate the use of tissue samples including artery or vein fragments in the methods for assaying angiogenesis as required by the claimed method, for example: US 5,856,184 [A] and Brown et al. [U]. The other references demonstrate the use of tissue samples either excluding tumor, artery or vein fragments

{Montesano et al. [V]} or including tumor fragments {Lugassy et al. [W]} as required by the presently claimed method.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the method for assaying angiogenesis *ex vivo* as the presently claimed with a reasonable expectation of success in observing angiogenesis in various tissue samples including that which are claimed because the prior art references teach the identical three-dimensional ex vivo systems and suggest the use of various factors which enhance or suppress angiogenesis. Thus, one of skill in the art would have been motivated to use the three-dimensional ex vivo systems for the benefit of studying angiogenesis in various tissues. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova,

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August 5, 2002.

IRENE MARX
PRIMARY EXAMINER